

Synthetic prostaglandin treatment in systemic cholesterol crystals embolism following endovascular aneurysm repair

Utilização de prostaglandina sintética no tratamento da embolia sistêmica de cristais de colesterol, após tratamento endovascular de aneurisma da aorta abdominal

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Introduction

Systemic atheroembolism is characterized by embolism of small cholesterol fragments, which lodge into small arterial ramifications of 100 to 200 μm diameter¹. Its incidence is not well defined, ranging from 0.15 to 3.4% in autopsy studies in general population and from 25 to 77% in autopsy studies of patients previously submitted to angiographic or open arterial procedures²⁻⁴. Atheroembolism is associated with atheromatosis of the aorta and iliac arteries in 80% of the cases². This phenomenon can occur as a result of spontaneous displacement of atheromatous material or, more commonly, following endovascular interventions, arterial operations, anticoagulation and thrombolytic therapy⁵. The objectives of this report are: to describe the catastrophic clinical course of a patient with diagnosis of cholesterol crystal embolism that spread to the intestines, kidney and lower limbs following endovascular aneurysm repair (EVAR) and to discuss and review the therapeutic options for this type of challenging clinical event.

Case Report

A hypertensive, diabetic, former smoker 76-year-old male, with a single kidney (left nephrectomy for kidney cancer, 10 years before) and non-dialytic chronic renal failure

(urea, Ur=57 mg/dL and creatinine, Cr=1.6 mg/dL), was admitted for abdominal aortic aneurysm (AAA) repair, which had been incidentally identified in a routine ultrasound exam. Preoperative computed tomography angiography (CTA) of the abdominal aorta and pelvis confirmed the presence of a fusiform infrarenal abdominal aortic aneurysm with 6.1x5.7 cm in its larger cross-sectional diameters, extensive mural thrombus and parietal calcification of the abdominal aorta and iliac arteries. Besides, the CTA analysis identified favorable anatomy for endovascular aneurysm repair (EVAR), the method selected by the medical team, considering that the patient was in his late 70s, with prior abdominal surgery and multiple associated medical conditions. The indication for treatment was based on the aneurysm size, as the patient presented no symptoms at diagnosis.

The surgical procedure was performed in a vascular interventional radiology unit, using general anesthesia, access through bilateral transverse inguinitomy, dissection and puncture of both common femoral arteries, without performing arteriotomy. Intraoperative angiography showed a considerable increase in the abdominal aorta caliber and moderate-to-severe parietal irregularities, well spread along all abdominal aorta and iliac arteries (Figures 1 and 2), compatible with diffuse atherosclerotic disease, without any other unusual finding. Then, a Zenithâ (Cook) modular bifurcation endoprosthesis, with main body of 30 mm proximal

Study carried out at the Instituto de Radiologia Intervencionista e Cirurgia Endovascular (INRADI) and the Service of Vascular and Endovascular Surgery of the Hospital Aliança – Salvador (BA), Brazil.

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diameter (TFFB – 30-82) and contralateral length of 20 mm diameter (TFLE – 20-56) was implanted. The selection of a graft with suprarenal fixation was based on the presence of mural thrombus, which involved about 40% of the proximal neck. The graft dimensions were defined through CTA imaging analysis – the exam had been performed less than 30 days before the admission -, with overlaying of 10% of its diameters at the anchoring sites in the aorta and common iliac arteries, as the medical team intended to preserve both hypogastric arteries. A total volume of 90 mL of non-ionic isosmolar iodinated contrast media was administered with an injector pump. The surgical procedure was performed without any complications, with estimated anesthetic duration of 60 minutes and surgery duration of 70 minutes. The patient presented diuresis of 250 mL in 2 hours. The lower limbs had symmetrical pulses and good perfusion. The endotracheal tube was removed in the operating room at the end of the procedure. He remained in the Intensive Care Unit (ICU) for less than 24 hours. After that, he was transferred to the ward and started on an oral diet on the 1st postoperative day (POD). On the 3rd POD, when hospital discharge was planned, the patient spiked a fever, without any changes in his general status. The medical team opted for in-hospital observation for an additional day.

Within the next 24 hours, the patient presented intermittent high fever. His laboratory exams showed increased leukocyte count (differential leukocyte count: 21,300 cells/mm³, with 81% neutrophils, 7% lymphocytes, 8% monocytes and 4% eosinophils), no changes in platelet count, sedimentation rate 152 mm/h, C-reactive protein: 11 mg/dL. Serum levels of Ur increased to 68 mg/dL and Cr to 2.1 mg/dL. The clinical picture of fever with leukocytosis led to the diagnosis of infection – unknown primary site – or systemic inflammatory response syndrome, following the endoprosthesis implantation. Blood and urine cultures were collected and empirical antimicrobial therapy started, with intravenous ampicillin associated with sulbactam, at the dose of 9 g daily, based on the Cr clearance.

After two days of antimicrobial therapy, the patient remained with fever, reduced urinary output and gradual increase of serum levels of Ur (72 mg/dL) and Cr (2.8 mg/dL), as well as respiratory discomfort, hypotension and abdominal distension with signs of peritoneal irritation and melena. Septic shock secondary to ischemic

colitis and peritonitis became the main suspected diagnosis. suspicions in terms of etiology of the clinical status. Rectosigmoid endoscopy showed two ulcerated lesions at the sigmoid – one of them with a central orifice, suggesting perforation. He was immediately taken to the operation room, with intraoperative confirmation of transmural sigmoid perforation. Rectosigmoidectomy was performed, further reinforcing the diagnostic hypothesis of septic shock secondary to ischemic colitis and peritonitis.

Despite intestinal resection and all supportive measures adopted in the ICU, the patient, got progressively worse, with daily fever, continuous increase in leukocyte count, metabolic acidosis, renal failure with oliguria requiring hemodialysis, ventilatory and introduction of vasopressor drugs (VPDs) as a result of refractory hypotension to volemic replacement. On the 8th hospitalization day, the patient presented sudden cyanosis in the toes of both feet (Figure 3), which was initially attributed to the septic shock and use of high doses of VPDs. Despite all signs and strong suspicion of septic shock secondary to ischemic colitis and peritonitis, the anatomopathological report of the surgical specimen surprised everyone, with the findings of small intestinal dilated submucosal arterial branches occluded and with neutrophils and cholesterol crystals, defining the diagnosis of cholesterol crystal embolism as the etiology of all systemic clinical presentations described above.

- Question 1: What are the differential diagnoses for cholesterol crystal embolism?
- Question 2: What therapeutic measures should be used in a rare clinical entity with relevant morbimortality and no standard treatment, such as atheroembolism?
- Question 3: Is it possible to use PGE1 in these situations?

Treatment

There is no consensus on the treatment of patients with systemic cholesterol microembolism. After the anatomopathological diagnosis of cholesterol crystal embolism, the therapeutic decisions were based on the experience of each specialist involved in the case. The initial therapeutic scheme included the association of corticosteroids, statin, cilostazol and low molecular weight heparin at therapeutic dose. However, the patient showed no sign of clinical and/or laboratorial



Figure 1. Abdominal aortography showing the presence of only one kidney to the right, as well as multiple parietal irregularities, compatible with diffuse atherosclerosis in this region.

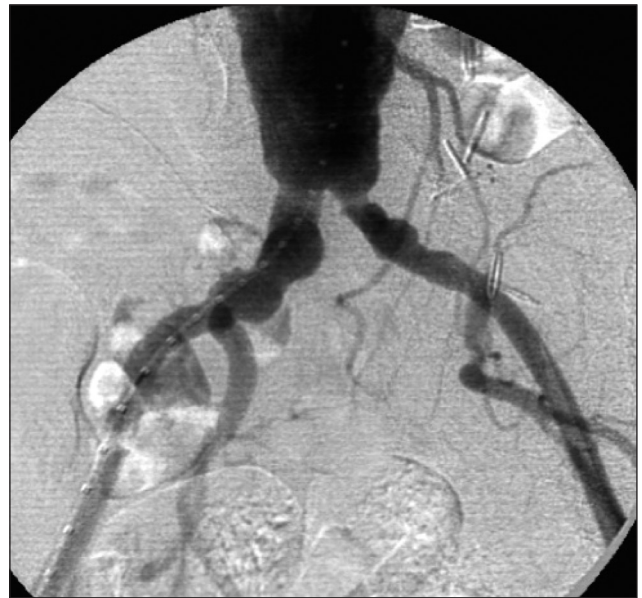


Figure 2. Pelvic arteriography showing aneurysmatic dilation of distal abdominal aorta, as well as diffuse parietal irregularities in iliac arteries, similar to the findings in Figure 1.

improvement after the introduction of these drugs. Instead, progressive worsening was observed under this scheme. With the evident ineffectiveness of the treatment and after extensive review of the medical literature, the team decided to interrupt the use of corticosteroids, cilostazol and enoxaparin; only statin was kept. In addition, isosorbide mononitrate (venous infusion of 40 mg each 8 hours) was introduced, associated with synthetic prostaglandin E1 or PGE1 (venous infusion of 20 µg on the 3 first days, followed by venous infusion of 40 µg, twice a day, for 4 weeks).

About 48 hours after the therapeutic changes described above, the first sign of clinical improvement was the fever decline. After that, slow regression of cyanosis in the toes was observed, until its complete resolution in 2 weeks, without loss of tissue integrity. Gradually, the patient was weaned off of vasopressor drugs, lung function improved and he was taken off of the mechanical ventilation. After 43 days, in which 13 sessions of hemodialysis were performed, kidney function was fully restored, with spontaneous diuresis and serum Ur and Cr returned to preoperative levels. About 120 days after EVAR, the patient was discharged from the hospital.



Figure 3. Cyanosis is observed in the distal segment of all toes, without alteration to forefoot perfusion. This clinical sign suggests occlusion of small digital arterial ramifications, without involvement of large-caliber arteries.

Discussion

The classic presentation of cholesterol crystal embolism (CCE) is marked by cool, painful and cyanotic toes in the presence of palpable distal pulses, referred to as

blue toe syndrome. This phenomenon is observed predominantly in white males over 60 years of age and with history of arterial hypertension, smoking, cardiovascular disease and renal failure⁶⁻⁸. However, in cases of disseminated CCE, the signs and symptoms are nonspecific, presenting subacute course (progression in 4 to 6 weeks) in most cases, suggesting the presence of a systemic disease, which makes its diagnosis more difficult. In the differential diagnoses, systemic conditions should be considered, such as low-output heart failure and septic shock, as well as connective tissue diseases, hypercoagulable states, intravascular coagulopathy, endocarditis or septic arthritis. However, when typical clinical presentations appear after endovascular procedures, arterial surgery, anticoagulation or use of thrombolytic drugs, the possibility of cholesterol crystal embolism should be taken into account.

Despite the unfavorable course and high mortality rates associated with progressive uremia, recovery from renal failure has been reported^{9,10} in similar cases to the one described in this report. Ischemic colitis has also been described as one of the intestinal complications after EVAR surgery, with incidence of around 2 to 5% of the cases¹¹. Devascularization of the left colon is the most frequent cause of this complication, while atheroembolism is a very uncommon cause. Bonamigo et al.¹¹ describe the occurrence of ischemic colitis in 12 patients (2% of the series). Two deaths occurred in this group, with atheroembolism being the cause of one of these deaths. Regarding the treatment of systemic atheroembolism, we can say that there are no consensus or guidelines on standardized clinical practices to be adopted, only scarce results reported. It is known that the main objectives in the atheroembolism treatment are the identification, suppression or excision of the atheroma plate that causes microembolism, local care of trophic lesions to reduce the chances of amputation, pain control, control of arterial pressure and of the systemic complications of atheroembolism, especially renal failure.

Several classes of drugs have been used in the treatment of atheroembolism, but with divergent results. These drugs include corticosteroids, anticoagulants, vasodilators, angiotensin-converting enzyme inhibitors, alpha-adrenergic antagonists and synthetic prostaglandin inhibitors¹²⁻¹⁴. Based on the information from a literature review, we decided to change the therapeutic

strategy, soon after the diagnosis of atheroembolism and failure of the initial treatment. Such information included:

- despite the description of corticosteroid use in patients with atheroembolism and progressive kidney failure, no consistent data were found on recovery of the kidney function with the use of this drug, in these circumstances¹⁵. In fact, some studies suggest higher incidence of morbidity, such as infectious, metabolic/nutritional complications and difficult lesion healing, as well as higher mortality rates with the use of high doses of corticosteroids^{2,15};
- the role of anticoagulation in the treatment of atheroembolism is also controversial. First, it should be noted that anticoagulants and thrombolytic drugs are described as factors that cause cholesterol microembolism. In addition, many authors have documented worsened clinical status after the introduction of heparin, as well as the absence of good results with the use of antiplatelet drugs in cases with atheroembolism^{8,16-18};
- the use of vasodilators, especially calcium channel blockers, relieves the ischemic pain of lower limbs secondary to vasospasm. However, the use of angiotensin-converting enzyme inhibitors should be avoided due to their negative effects on kidney function¹⁹;
- the use of high doses of statins is defended by several authors, as they stabilize the cholesterol-rich atheroma plates, causing improved kidney function and ischemia of lower limbs, due to their anti-inflammatory and immunomodulator properties²⁰;
- prostaglandin E₁ (PGE₁) is a substance of high biological activity and different properties, such as: vasodilating action, inhibition of platelet aggregation, fibrinolysis activation, modulation of cell proliferation, fibrinogenesis and hemorheological activity¹³. Its use has shown to be effective in the treatment of peripheral occlusive arterial disease²¹ and in cases of pulmonary hypertension and Raynaud's phenomenon^{21,22}.

Positive effects of both PGE₁²³ and prostacyclin^{24,25} on kidney function have been reported. The vasodilating action of synthetic prostaglandins on afferent and efferent kidney arterioles, with significant increase in renal plasma flow, without affecting glomerular filtration rate and

plasma renin activity, as well as other described properties, seem to explain its effectiveness in the treatment of kidney failure secondary to atheroembolism²⁴.

Conclusions

Although atheroembolism affects only 0.03% of hospitalized patients⁴, this is a clinical entity of difficult diagnosis, with severe clinical complications and mortality rates ranging from 64 to 81%². Besides the unfavorable results, there is no specific or standard treatment for atheroembolism. PGE₁, when used in peripheral vascular diseases, is more commonly indicated for the treatment of patients with POAD. Insufficient data are available about its use in cases of systemic atheroembolism and progressive kidney failure. However, the authors tried this drug after an ineffective course of therapy with corticosteroids, statin and anticoagulants, which are more frequently used in these situations. After the introduction of PGE₁, the patient presented a slow, but evident clinical improved, with recovery of kidney function to preoperative levels and restored organic functions. We cannot conclude that PGE₁ was the only substance that caused the patient's complete recovery. However, despite the limitations and observational characteristics of this report, we believe that the use of PGE₁ can be justified in situations like the one described in this study, and that this therapy can be a reasonable choice for further studies on the treatment of atheroembolism.

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Writing: MVB, AG, PSAP
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